REMARKS

Claims 1, 3-5, 7, 8, 10-23 are pending in this application. Claims 2, 6 and 9 have been cancelled. Claims 10-23 have been withdrawn. Claims 1, 3-5, 7 and 8 stand rejected under §§ 102(b), 103(a) and/or 112, second paragraph.

In an effort to simplify prosecution and expedite allowance, Applicants have amended claims 1, 3-5, 7 and 8 to clarify the claims and overcome the rejections. Support for these amendments (i.e., a cell-free composition comprising a complex) may be found in the claims as previously presented and originally filed and throughout the specification. In addition, support for these amendments may be found on page 3, lines 21-24; page 5, lines 3-6; page 9, lines 8-11; page 36, lines 13-14; and page 37, lines 12-14. It is believed that no new matter has been added.

Rejection under 35 U.S.C.§ 112, Second Paragraph

The Examiner rejected claims 1 and 3-5 under Section 112, second paragraph for failing to point out and distinctly claim the subject matter for which applicant regards as his invention. Without agreeing to the accuracy of the Examiner's conclusion, Applicants hereby amend claims 1 and 3-5 to clarify them. The amendments should overcome the Examiner's rejection. Applicants therefore earnestly request entry of the proposed amendment and withdrawal of the rejection after considerations.

Rejection under Section 102(b)

The Examiner rejected claims 1, 3-5, 7 and 8 under 35 U.S.C. § 102(b) as being inherently anticipated by Matsuzaki (FEBS Letters (1996) 305-8) in view of Toker et al., *J. Biol. Chem.*, (2000) 275:8271-4). The Examiner argued that Matsuzaki teaches a purified RAC-protein kinase (PKB/Akt) which has a molecular weight of about 58kDa. The Examiner did not specify which property of the claimed invention is inherently disclosed in Toker et al., but seems to have argued that the PKB Ser 473 kinase activity in PBK/Akt is inherently disclosed because Toker et al. shows that the PBK/Akt, when associated with cellular proteins, has PKB Ser 473 kinase activity. Although the Examiner admitted that the prior art does not disclose the difference between the purity of the claimed composition and the crude extract of HEK 293 cells, the apparent molecular weight of the protein when fractionated by gel filtration chromatography

when associated with cellular proteins or the presence of additional protein of the claimed molecular weight, the Examiner nevertheless argued that the burden is shifted to Applicants to provide evidence establishing unobvious difference between the claimed composition and the prior art.

In response to the Final Office Action and Advisory Action, Applicants have amended the claims and respectfully request entry of the proposed amendments. Applicants respectfully submit that the claims are not anticipated by Matsuzaki in view of Toker et al.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Although extrinsic evidence such as a second reference may be used to show an inherent characteristic within the teaching of the primary reference, "[the second reference] must make clear that the missing descriptive matter is necessarily present in the thing described in the [primary] reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

Here, claim 1 and its dependent claims are directed to a cell-free composition which comprises a protein complex which has PKB Ser 473 kinase activity and an apparent molecular weight of 450-650 kDa. Although Matsuzaki teaches a purified RAC-protein kinase, Matsuzaki does not disclose a protein kinase or a complex having a molecular weight of 450-645kDa and has PKB Ser 473 kinase activity. Although Toker et al. shows that PBK/Akt has PKB Ser 473 kinase activity, the accuracy of this has been questioned by those skilled in the art. As cited in Applicants' previous response, Hill et al., *J. Biol. Chem.* (2001) 276(28):25643-6 shows that staurosporine, a broad-specificity kinase inhibitor, potently inhibited PDK1 activity without affecting Ser 473 phsophorylation, which suggests that phosphorylation of Ser473 of PKB is via a distinct Ser-473 kinase and not through PDK1 or PKB activity. In fact, Alex Toker himself acknowledges such skepticism in a later article titled "Akt signaling: A Damaging Interaction Makes Good", *Trends in Biochemical Sciences*, (2008) 33(8):356-359 ("Second Toker Article")[1]

[1] It is noted that the Second Toker Reference is cited to support an argument against that raised by the Examiner during the final office action and to provide information about the state of the art after the filing date of the current

where he recognizes that the "[i]nitial findings that PDK-1, the integrin-linked kinase or Akt itself was the Ser473 kinase [ ] were met with considerable skepticism" and acknowledges a study by the Sabatini group which shows the relevant Ser 473 kinase. *Id.* at p.358. These two articles, therefore, suggest that PKB/Akt does not autophosphorylate. This conclusion (i.e., that PKB/Akt does not autophosphorylate) is also well known/accepted in the art. As such, the Examiner has not established that PBK/Akt has PKB Ser473 kinase activity.

Even if the PBK/Akt arguably has PKB Ser 473 kinase activity, the prior art cited does not disclose, explicitly or inherently, the molecular weight limitation of the claims. The PKB/Akt used in Matsuzaki and Toker et al. is a purified protein. The Examiner admitted that the protein kinase taught by Matsuzaki has a molecular weight of about 58 kDa, which falls outside of the limitation of the present claims (by almost a factor of 10). The Examiner also admitted that the prior art does not disclose the apparent molecular weight of the crude extract of HEK 293 cells. Nothing in the prior art therefore suggests a complex having a molecular weight of 450-650kDa and PKB Ser 473 kinase. In fact, prior to the filing of the current application, it is not known that Ser473 kinase operates via a multi-subunit/protein complex as disclosed in the currently claimed invention. This discovery, however, is consistent with the later finding by the Sabatini group as discussed in the Second Toker Article, which shows that the relevant Ser 473 kinase, in fact, operates as complex. Applicants respectfully submit that the prior art references do not explicitly or inherently disclose every element of the claimed invention. Withdrawal of the rejections under 35 U.S.C. § 102 is earnestly requested.

Rejection under Section 102/103

The Examiner rejected claims 1, 3-5, 7 and 8[2] under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Dedhar (US 6,338,958). The Examiner argued that Dedhar anticipates the currently claimed invention because Dedhar teaches a composition comprising a purified integrin-linked kinase (ILK) which

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application and therefore should not be construed to be an admission that the information cited is material to patentability or prior art.

[2] The Examiner stated that claim 9 is rejected under 102(b), but claim 9 was previously cancelled. It is believed that this is a typographical mistake and the Examiner meant claim 8 is rejected under this section.

has a molecular weight of about 59kDa and has PKB Ser 473 kinase activity when associated with cellular proteins. Applicants respectfully disagree. The Examiner admitted that ILK of the Dedhar reference has a molecular weight of 59kDa. The cellular proteins of the Dedhar reference to which the ILK associate have a molecular weight of 32kDa and 70kDa. *See* US 6,339,958, column 22, lines 1-2. Therefore, the ILK complex of the Dedhar reference does meet the 450-650kDa limitation of the claimed invention. The Examiner argued that the present claims do not recite a single protein but a protein which possesses PKB activity when associated with other cellular proteins. While a cellular-protein-associated PKB Ser 473 kinase is not a single protein *per se*, the claims nevertheless require the kinase complex to have a molecular weight of 450-650kDa. PKB Ser473 kinase, when not associated with other cellular protein, only has a molecular weight of about 59kDa as seen in the prior art. Because the Dedhar reference does not disclose a kinase which, when associated with other cellular-protein, has the molecular weight as required by the presently claimed invention, it does not anticipate claims 1, 3-5, 7 or 8.

In the alternative, the Examiner argued that Dedhar renders the presently claimed invention obvious. According to the Examiner, Dedhar teaches that HEK 293 cells may be transfected with constructs comprising ILK and the protein expressed from this may be purified from a lysate using any way known in the art, including size exclusion chromatography, resulting in a purified protein, and as such, one skilled in the art would be motivated to purify an ILK expressed in HEK 293 cells to arrive at the claimed composition as protein purification is well known in the art. Applicants respectfully disagree. Even though Dedhar et al. discloses that the lysate may be purified by any conventional methods, there is nothing in the Dedhar reference that suggests a protein having a molecular weight of 450-650kDa so as to motivate one skilled in the art to isolate this complex rather than any other size protein or complex. In addition, the specification of the present invention discloses fairly controlled and specific purification steps, e.g., treating the plasma membrane fraction with a buffer comprising a detergent that is preferably non-ionic detergent and starting with a high capacity and relatively low selectivity purification step, followed by steps having intermediate capacity and/or selectivity, followed by steps having low capacity and high selectivity so as to isolate a partially purified PKB Ser473 kinase rather than the further purified Ser473 kinase that resulted in a loss of activity. *See*

Specification, page 12, lines 17-29 and from page 13, line 28 to page 18, line 15; *See also* Specification, page 29-38, Examples 1-4. Therefore, one skilled in the art, in practicing the invention as disclosed in the Dedhar reference, would not arrive at the presently claimed invention, or be motivated to alter the procedure of Dedhar to arrive at the presently claimed invention. Not only that, Example 7 of the present application shows that ILK of the Dedhar reference lacks PKB Ser 473 kinase activity. As such, the Dedhar does not disclose all of the elements of the claimed invention nor does it motivate one skilled in the art to modify the procedure disclosed in that reference to arrive at the presently claimed invention. Applicants, therefore, respectfully request withdrawal of the rejections under section 102(b)/103(a).

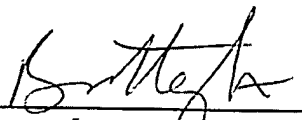
CONCLUSION

Applicant respectfully submits that the claims are now in condition for allowance and notification to that effect is earnestly requested.

It is believed no fee, other than the fees for filing an RCE and for an extension of time, is required. Should this be incorrect, the Commissioner is authorized to charge any additional fees, or credit any overpayment, to deposit account No. 50-4255.

Respectfully submitted,

Date December 9, 2008



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